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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,831	12/21/2001	Paul Richard Vaughan	Q-67867	4805

23373 7590 01/26/2004

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,831	VAUGHAN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/297,269.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 21 December 2001, which claims befit of U.S. application 09/297,269 filed 28 April 1999 as the U.S. national stage of international application PCT/AU97/00721, and claims benefit of Australian patent applications PO 3310 filed 29 October 1996 and PO 4306 filed 19 December 1996. The preliminary amendments filed 21 December 2001, 19 June 2002 and 12 November 2003 have been entered. Claims 31-35 are presently pending.

Election/Restrictions

Applicant's election without traverse of Group II (claims 31-35) in the Paper filed 12 November 2003 is acknowledged.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Rule 1.825(a) states, "Any amendment to a paper copy of the 'Sequence Listing' (§ 1.821(c)) must...include a statement that the substitute sheets include no new matter." A complete reply to this Office Action must include a statement that the sequence listing filed 19 June 2002 adds no new matter.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 31-35 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. In their broadest embodiment, the claims are directed to a hydroxylated triple helical protein comprising a polypeptide and a biomaterial comprising said protein. Because they do not particularly point out any non-naturally occurring differences between the claimed products and naturally occurring products, the claims encompass any naturally occurring hydroxylated polypeptide comprising a triple helix (e.g., collagen) or any biological material comprising said protein. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a hydroxylated triple helical protein wherein the protein is a collagen, does not reasonably provide enablement for the broad scope of polypeptides encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a protein comprising a hydroxylated triple helix wherein said protein can be any polypeptide or synthetic polypeptide or peptide represented by the formula set forth in claim 31 and, in some embodiments, wherein the GlyXY containing repeat domain comprises no more than 10-300 amino acids or wherein the GlyXY domain is limited to having an amino acid length of at least three times the combined length of domains E and F. In the broadest embodiment, the polypeptide of the claims can be any polypeptide comprising a hydroxylated residue, a triple helix and at least 2 GlyXY triplets which can be separated by an unlimited number of amino acids (i.e., 'E' or 'F' of the formula set forth in claim 31). Thus, the claims are generic to a vast array of hydroxylated triple helical proteins. As the enabling disclosure must teach the skilled artisan how to use the full scope of the claimed invention, it is incumbent upon the instant specification to set forth the process of using the genus of products claimed in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the same. With regard to using the claimed

polypeptides, the specification teaches that the products may be used in a wide range of applications including bioimplant production, soft and hard tissue augmentation, wound/burn dressing, sphincter augmentation fur urinary incontinence and gastric reflux, periodontal disease, vascular grafts, drug delivery systems, cell delivery systems for natural factors and as conduits in nerve regeneration (see e.g., page 29). Thus, the specification must teach the skilled artisan how to use the claimed peptides and proteins as biomaterials or therapeutics.

State of the prior art and level of predictability in the art: Although the application of collagens in the manufacture of biocompatible materials (e.g., artificial skin) having a variety of therapeutic applications is known in the art, the art does not teach that any polypeptide comprising a hydroxylated residue, a triple helix and at least 2 GlyXY triplets is generally therapeutic. In fact, the art teaches that the properties of collagen aggregates which make them useful for such applications as bioimplant production, soft tissue augmentation and wound/burn dressings are dependent upon their ability to form strong structural matrices. The fact that a variety of mutations have been found to disrupt the aggregation of collagen fibrils (see e.g., Brodsky *et al.* (1995) *FASEB J.* 9:1537-1546, especially the section entitled "Mutations in Triple Helices") provides evidence that the ability to form therapeutically useful matrices is not a general property of hydroxylated triple helical proteins. As the art is silent with regard to therapeutic application of hydroxylated triple helical proteins other than collagen, the skilled artisan must rely on the teachings of the instant specification for guidance on how to use a therapeutic product comprising an hydroxylated triple helical protein other than collagen.

Amount of direction provided by the inventor and existence of working examples: With regard to using therapeutic products comprising hydroxylated triple helical proteins other than

collagens, the teachings of the specification provide no guidance beyond what was already available in the art. Most of the teachings in the specification are concerned with producing a collagen in yeast. With regard to therapeutic application of the proteins, the specification merely provides broad general statements that the products may be used in a wide range of applications including bioimplant production, soft and hard tissue augmentation, wound/burn dressing, sphincter augmentation fur urinary incontenence and gastric reflux, periodontal disease, vascular grafts, drug delivery systems, cell delivery systems for natural factors and as conduits in nerve regeneration (*Id.*). The specification provides no guidance with regard to how to use those polypeptides encompassed by the claims that lack the structural integrity of collagen. Further, the specification provides no guidance that would enable the skilled artisan to identify those hydroxylated triple helical proteins that could be used therapeutically without having to engage in undue experimentation to make and test each of the polypeptides encompassed by the claims.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, one of ordinary skill in the art would not be able to use the full scope of the claimed invention without having to engage in undue experimentation. Although the art teaches that collagens are therapeutically useful, neither the art nor the instant specification teaches how any protein having the structure of a hydroxylated triple helical protein can be applied therapeutically. The skilled artisan armed with no more than the teachings available at the time of filing would not know how to use the vast majority of therapeutic products encompassed by the claims, and would not be able to distinguish which hydroxylated triple helical proteins could be substituted for collagen in therapeutic applications without having to resort to blind trial and error experimentation to make

and test each of the proteins encompassed by the claims. Given the tremendous scope of the claims this would clearly require undue experimentation. Therefore, practicing the claimed invention commensurate with its full scope would require undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because, although the preamble of claim 31 recites that the claimed polypeptide is an hydroxylated triple helical protein, only a small fraction of the peptides described by the formula set forth in claim 31 would form a triple helix. As described above, the structural limitations set forth in claims 31-33 embrace any peptide comprising at least two GlyXY domains, one of which comprises proline at the Y position, wherein the at least two GlyXY domains can be separated by an unlimited number of amino acids (i.e., 'E' or 'F' of the formula set forth in claim 31). That is, in the broadest embodiment the repeat unit $Z=(E)_q$-$(GlyXY)_l$-$(F)_r$, wherein q is 1 to ∞ and r= 1 to ∞. Clearly, the vast majority of peptides represented by the formula set forth in the claim would not form a triple helix. As the peptides encompassed by the formula are tremendously diverse and lack a required structural element that could be correlated to the formation of a triple helix, there is no apparent nexus between the

limitations of the formula and the structural limitation set forth in the preamble. Thus, it is unclear how the formula should be interpreted as further limiting the claimed subject matter.

The claims are further indefinite in reciting "$(GlyXY)_n$" in the 24th and 29th lines of claim 31. The subscript "n" is not defined in the claim and it is unclear how the term should differ from "$(GlyXY)_i$" which appears earlier in the claim.

Claim 32 is further indefinite in reciting, "domain Z comprises no more than 10 to 300 GlyXY repeats". If the domain Z is limited to comprising no more than 10, then it is unclear why the claim is further limited to comprising no more than 300, as this would be inherent. On the other hand, if the protein of the claim can comprise up to 300 repeats it cannot be limited to comprising no more than 10. Alternatively, the claim might be read as limited to comprising only those proteins wherein the number of repeats falls within the range of 10 to 300, however it is unclear whether this is what Applicant intends. Thus, it is unclear what is being claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Fields *et al.* (1996) *Lett. Peptide Sci.* 3:3-16.

Fields *et al.* teaches a variety of artificial peptides comprising Gly-Pro-Hyp, wherein Hyp is hydroxyproline, which form triple helixes (see especially Table 1 and Figure 1 and the captions thereto). Furthermore, the peptides described by Fields *et al.* falls within the genus defined by the formula set forth in claim 31. Thus, Fields *et al.* meets the limitations of the base claim 31. Further, Fields *et al.* explicitly teaches repeat domains of 9 (e.g., α1(IV)531-543) to 13 (e.g., α1(IV)1263-1277) repeats according to claim 32, and repeat domains which are at least three times greater than the combined length of the E and F domains comprised by the peptides (e.g., α1(IV)1263-1277, α1(I)1263-1277772-786, etc.) according to claim 33.

As Fields *et al.* teaches each of the limitations of the instant claims, the claims are anticipated by Fields *et al.*

Claims 31, 32 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Silver *et al.* (1992) U.S. Patent No. 5,171,273.

Silver *et al.* teaches an hydroxylated triple helical protein (i.e., bovine type I collagen, see especially column 11, fourth full paragraph) according to claims 31 and 32. Furthermore, throughout the disclosure Silver *et al.* teaches that the protein can be used in biomaterials and therapeutic products according to claim 34. Thus, the teachings of Silver *et al.* anticipate the limitations of the instant claims.

Claims 31 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by any one of Swiss-Prot database entries P02745 (1986), P07714 (1988), P35247 (1994), P11226 (1989), P23805 (1991), or P21757 (1991).

Each of the Swiss-Prot database entries teach a polypeptide comprising a collagen repeat domain which would form an hydroxylated triple helix and thus meets the limitation of an hydroxylated triple helical protein comprising a polypeptide. Furthermore, the proteins described in the Swiss-Prot entries fall within the genus defined by the formula set forth in claim 31. Thus, Fields *et al.* meets the limitations of the base claim 31. Each of the Swiss-Prot entries also comprise a repeat domain (i.e., Z domain) comprising between 10 and 300 repeats according to clam 32. Thus, the art teaches proteins comprising all of the limitations of the instant claims 31 and 32.

Claims 31-35 are rejected under 35 U.S.C. 102(e) as being anticipated by St. Pierre *et al.* U.S. Patent No. 5,856,308 (filed 27 September 1996).

St. Pierre *et al.* teaches an hydroxylated triple helical protein having the characteristics set forth in Formula A and described in the section entitled "1. Collagen Mimics" beginning in column 3. Many of the species described by the formula of St. Pierre *et al.* meet the limitations of the instant hydroxylated triple helical protein according to claims 31-33 and thus anticipated the claims. For example, when n=28, x=0 and w=1, the Formula A of St. Pierre *et al.* anticipates all of the limitations of claims 31-33. Further, St. Pierre *et al.* teaches that the hydroxylated triple helical proteins disclosed therein are to be used in biomaterials or therapeutic products according to claims 34 and 35 (see especially the third full paragraph in column 3. As the products described by St. Pierre *et al.* comprise all of the limitations of the instant claimed invention, the claims are anticipated by St. Pierre *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

DAVID GUZO
PRIMARY EXAMINER